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PATENT APPLICATION
Docket No.: KIR96-01

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellants: Michael J. Elliott, Ravinder N. Maini and Marc Feldmann

Application No.: 08/602,272 Group Art Unit: 1642

Filed: February 16, 1996 Examiner: N. Johnson

For: METHODS OF PREVENTING OR TREATING THROMBOSIS WITH TUMOR NECROSIS FACTOR ANTAGONISTS (As Amended)

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231

on 9-28-99 Sandra Vautour
Date Signature

Sandra Vautour
Typed or printed name of person signing certificate

BRIEF ON APPEAL

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Brief on Appeal is submitted pursuant to the Notice of Appeal mailed on March 29, 1999 and received in the U.S. Patent and Trademark Office on April 1, 1999, in the above-referenced patent application. The fee for filing this Brief on Appeal is enclosed. A four-month

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extension of time for submission of this Brief is requested. A Petition for Extension of Time and the appropriate fee are being filed concurrently with this Brief.

This Brief is submitted in support of the appeal of the Examiner's final rejection of Claims 6, 8-10, 12-15, 29-32 and 34-37 as set forth in the Office Action made final, which was mailed from the Patent Office on September 29, 1998.

Each of the requirements set forth in 37 C.F.R. § 1.192(c) follow under the separate headings.

I. REAL PARTY OF INTEREST

The real parties of interest are the Kennedy Institute of Rheumatology, One Aspenlea Road, Hammersmith, London W6 8LH, England, pursuant to assignments from each of the inventors of the subject application, and Centocor, Inc., 200 Great Valley Parkway, Malvern, Pennsylvania 19355, licensee of the subject matter described in the subject application.

II. RELATED APPEALS AND INTERFERENCES

Appellants, the undersigned Attorney, Assignee and Licensee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 6, 8-10, 12-15, 29-32 and 34-37 are pending and subject to this appeal. Claims 11 and 33 were cancelled by Appellants in Amendment B, filed July 9, 1998. Claims 1-5 and 7 were cancelled by Appellants in Amendment A, filed September 29, 1997. Claims 16-28 and 38-50 were withdrawn from further consideration by the Examiner for being drawn to non-elected species. The pending claims, as they stood upon final rejection, are presented in the Appendix to this Brief.

IV. STATUS OF AMENDMENTS

A Reply After Final was mailed to the Patent Office on April 21, 1999 and considered by

the Examiner. No amendment to the claims or specification was presented in this submission.

In the Advisory Action dated May 28, 1999 (Paper No. 19), the Examiner indicated that the Reply After Final would be entered upon the filing of an appeal. The Examiner also indicated in the Advisory Action that the arguments presented in the Reply After Final had overcome the rejection of Claims 14-15 and 36-37 under 35 U.S.C. § 112, second paragraph, in regard to the clarity and definiteness of the term "cA2", and the rejection of Claims 6 and 29 under 35 U.S.C. § 112, first paragraph, in regard to the enablement of "TNF antagonist". It is noted that a Notice of Appeal was filed in the subject application on April 1, 1999.

V. SUMMARY OF INVENTION

The present invention relates to methods of treating or preventing thrombosis in an individual in need thereof comprising administering a therapeutically effective amount of a TNF antagonist to the individual (Claims 6, 8-10 and 12-15). The present invention also relates to methods of decreasing plasma fibrinogen in an individual suffering from or at risk of thrombosis comprising administering a therapeutically effective amount of a TNF antagonist to the individual (Claims 29-32 and 34-37).

The TNF antagonist can be an anti-TNF antibody or antigen-binding fragment thereof (Claims 8-10, 12-15, 30-32 and 34-37). The antibody can be a chimeric antibody, a humanized antibody or a resurfaced antibody (Claims 9, 12-15, 31 and 34-37). The antibody can bind to one or more epitopes included in amino acid residues of about 87-108 or about 59-80 of hTNFα (Claims 10, 13, 32 and 35) or competitively inhibit binding of TNFα to monoclonal antibody cA2 (Claims 14, 15, 36 and 37). In a particular embodiment, the antibody is cA2 (Claims 15 and 37).

VI. ISSUE

The sole issue on appeal is whether the Examiner erred in rejecting Claims 6, 8-10, 12-15, 29-32 and 34-37 under 35 U.S.C. § 112, first paragraph, as non-enabled by the specification with respect to the breadth of thrombosis treated or prevented with TNFα antagonists.

VII. GROUPING OF CLAIMS

With respect to the issue to be decided, the claims stand or fall together.

VIII. APPELLANTS' ARGUMENT

Claims 6, 8-10, 12-15, 29-32 and 34-37 have been rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's assessment, the specification does not enable one skilled in the art to treat or prevent thrombosis of all origins with a reasonable expectation of success. Advisory Action dated May 28, 1999 (Paper No. 19), at Item 4. Appellants respectfully disagree.

Claims 6, 8-10 and 12-15 relate to methods of treating or preventing thrombosis in an individual in need thereof comprising administering a therapeutically effective amount of a TNF antagonist to the individual. Claims 29-32 and 34-37 relate to methods of decreasing plasma fibrinogen in an individual suffering from or at risk of thrombosis comprising administering a therapeutically effective amount of a TNF antagonist to the individual.

The standard for enablement under 35 U.S.C. § 112, first paragraph, is whether the claimed invention can be practiced without undue experimentation given the guidance presented in the specification and what was known to the skilled artisan at the time the subject application was filed. A specification which contains a teaching of how to make and use the full scope of the claimed invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). Further, "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." In re Armbruster, 185 U.S.P.Q. 152, 153 (C.C.P.A. 1975).

The specification teaches that thrombosis can be treated or prevented in an individual by administering a TNF antagonist to the individual in therapeutically effective amounts (see, e.g., page 6, lines 19-20). Examples of TNF antagonists, including anti-TNF antibodies, are provided in the specification, for example, at page 7, line 9 to page 29, line 7. Guidelines for route of

administration and dosages are provided in the specification, for example, at page 29, line 9 to page 32, line 4.

The specification discloses at page 4 that many patients with rheumatoid arthritis (RA) ultimately die from cardiovascular and cerebrovascular diseases (see page 4, lines 2-4). The specification also discloses that persistently elevated plasma fibrinogen and/or platelet levels are major contributors to the excess cardiovascular and cerebrovascular mortality seen in RA patients (see page 4, lines 4-9). See also Wolfe *et al.*, *Arthritis Rheum.*, *37*:481-494 (1994); reference AT on Form PTO-1449; attached hereto as Exhibit 1.

The Examiner acknowledges that the specification teaches that the administration of anti-TNF antibodies to rheumatoid arthritis patients results in a decrease in elevated fibrinogen levels to a range closer to normal and that inhibition of the biological activity of TNFα reduces fibrinogen and platelet levels in individuals with active rheumatoid arthritis (see, e.g., page 2, lines 14-18; page 5, lines 6-10; and page 36, Table 2 of the specification). Office Action dated September 29, 1998 (Paper No. 15), at page 4, lines 14-18. Given these results, one skilled in the art on the effective filing date of the application would reasonably have expected anti-TNF antibodies to be effective in the treatment of thrombosis, particularly since elevated fibrinogen and platelet levels play integral roles in thrombosis. That is, one skilled in the art would reasonably have expected that a means of decreasing fibrinogen levels would likely be effective in the treatment of thrombosis. No evidence to support a contrary conclusion has been presented. Thus, Appellants respectfully submit that the guidance provided in the specification is sufficient to enable the skilled artisan to practice the full scope of the claimed methods with a reasonable expectation of success and without undue experimentation.

The Examiner has also alleged that:

> There is absolutely no evidence of record that outside of the context of the pathological state of rheumatoid arthritis, that anti-TNF antibodies influence fibrinogen level and thrombosis. For example, the main presenting symptoms of rheumatoid arthritis are pain, stiffness, swelling and loss of function. Similar symptoms of rheumatoid arthritis are also the main presenting symptoms in another form of arthritis, osteoarthritis. However, from studies of model systems for both rheumatoid and osteoarthritis, it is art accepted that anti-TNF antibodies would have a modulatory effect in only rheumatoid arthritis and not osteoarthritis

(see U.S. Patent 5,698,195 (col. 38, lines 46-55). Thus, anti-TNF antibodies do not broadly inhibit joint pain and stiffness, from all causes.

Appellants respectfully disagree with this assessment. It appears that this argument is being relied upon for providing evidence that one skilled in the art would not readily accept that the specification provides enabling support for the claimed methods.

It is agreed that rheumatoid arthritis is a distinct disease, with unique pathological parameters that are known to be associated with an increased production of TNF. This, however, would not have led one of ordinary skill in the art to reasonably conclude that a means of decreasing a component which plays an integral role in thrombosis, i.e., fibrinogen levels, would not be effective in the treatment of thrombosis. No evidence to support a contrary conclusion has been presented.

U.S. Patent No. 5,698,195 discloses in the passage referenced by the Examiner (i.e., at col. 38, lines 46-55) that, in evaluating whether TNFα is a suitable therapeutic target for the therapy of rheumatoid arthritis, the effects of anti-TNF antibody and peptides on rheumatoid joint cultures and osteoarthritic cell cultures were studied. The referenced passage reports that the anti-TNF antibody abolished IL-1 production, showing TNFα as a suitable therapeutic target for the therapy of rheumatoid arthritis, and refers to Brennan *et al.* (*Lancet, 11*:244-247 (1989); attached hereto as Exhibit 2) (col. 38, lines 50-54).

The Brennan *et al.* reference reports the results of a study in which the effect of anti-TNF antibodies on synovial cell IL-1 production was investigated in 7 patients with rheumatoid arthritis and in 7 patients with osteoarthritis. Brennan *et al.* found that synovial cell IL-1 production was significantly reduced by anti-TNF antibody in cultures from patients with rheumatoid arthritis (see, e.g., page 246, Table II). In cultures from 6 of the 7 patients with osteoarthritis (i.e., patients 1, 2 and 4-7), Brennan *et al.* found that spontaneous IL-1 production was low despite high concentrations of TNFα (see, e.g., page 245, Table I; and page 254, col. 2, lines 17-25), and IL-1 production was not inhibited by anti-TNF antibody (see, e.g., page 246, Table II). In the culture from the remaining patient with osteoarthritis (i.e., patient 3), synovial cell IL-1 production was comparable to synovial cell IL-1 production in the rheumatoid arthritis cultures (see, e.g., page 245, Table I). In addition, similar to that found in cultures from patients

with rheumatoid arthritis, synovial cell IL-1 production was inhibited by anti-TNF antibody in culture from this patient with osteoarthritis (i.e., patient 3) (see, e.g., page 246, Table II; and page 246, col. 1, lines 15-20).

These results are said to indicate that inhibition of IL-1 activity by anti-TNFα antibody in culture was only apparent with a high initial IL-1 concentration (Brennan *et al.*, sentence bridging pages 246 and 247). Thus, in osteoarthritis synovial cultures where the initial IL-1 concentration is low, anti-TNFα antibody would not be expected to inhibit IL-1 activity. However, in osteoarthritis synovial cultures where the initial IL-1 concentration is high, anti-TNFα antibody would be expected to inhibit IL-1 activity. Accordingly, Brennan *et al.* (and, as such, Le *et al.*) do not support the Examiner's assertion that "it is art accepted that anti-TNF antibodies would have a modulatory effect in only rheumatoid arthritis and not osteoarthritis". Furthermore, the claims do not embrace the treatment of osteoarthritis or the inhibition of "joint pain and stiffness, from all causes." Thus, the Examiner's assertions are not relevant to the claimed subject matter.

There is nothing of record which might suggest that the guidance provided in the specification would be insufficient to enable the skilled artisan to practice the full scope of the claimed methods without undue experimentation and with a reasonable expectation of success. Accordingly, Appellants submit that the specification enables one skilled in the art to treat or prevent thrombosis with a reasonable expectation of success and without undue experimentation.

CONCLUSION

It is respectfully requested that the rejection be reversed and that the claims be allowed. This Brief is being filed in triplicate.

Respectfully submitted,

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Date: September 28, 1995

APPENDIX

REJECTED CLAIMS OF 08/602,272

6. A method of treating or preventing thrombosis in an individual in need thereof comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to the individual.

8. A method of Claim 6 wherein the tumor necrosis factor antagonist is an anti-tumor necrosis factor antibody or antigen-binding fragment thereof.

9. A method of Claim 8 wherein the antibody is selected from the group consisting of: a humanized antibody and a resurfaced antibody or antigen-binding fragment thereof.

10. A method of Claim 8 wherein the antibody binds to an epitope included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNFα.

12. A method of Claim 8 wherein the antibody is a chimeric antibody, wherein said chimeric antibody comprises a non-human variable region specific for TNF or an antigen-binding portion thereof and a human constant region.

13. A method of Claim 12 wherein the chimeric antibody binds to an epitope included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNFα.

14. A method of Claim 12 wherein the chimeric antibody competitively inhibits binding of TNFα to monoclonal antibody cA2.

15. A method of Claim 14 wherein the chimeric antibody is monoclonal antibody cA2.

29. A method of decreasing plasma fibrinogen in an individual suffering from or at risk of thrombosis comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to the individual.

30. A method of Claim 29 wherein the tumor necrosis factor antagonist is an anti-tumor necrosis factor antibody or antigen-binding fragment thereof.

31. A method of Claim 30 wherein the antibody is selected from the group consisting of: a humanized antibody and a resurfaced antibody or antigen-binding fragment thereof.

32. A method of Claim 30 wherein the antibody binds to an epitope included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNFα.

34. A method of Claim 30 wherein the antibody is a chimeric antibody, wherein said chimeric antibody comprises a non-human variable region specific for TNF or an antigen-binding portion thereof and a human constant region.

35. A method of Claim 34 wherein the chimeric antibody binds to an epitope included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNFα.

36. A method of Claim 34 wherein the chimeric antibody competitively inhibits binding of TNFα to monoclonal antibody cA2.

37. A method of Claim 36 wherein the chimeric antibody is monoclonal antibody cA2.